# Nanobioconjugates for signal amplification

Subjects: Nanoscience & Nanotechnology

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Amplification of signals from devices as a result of their interaction with a target analyte is of paramount importance. It may impact on the sensitivity and detection limits of the device. This review provides some examples of nanobioconjugates (biomolecules conjugated with nanomaterials), current challenges and future perspectives for the amplification of signals in electrochemical biosensing based on nanobioconjugates.

nanobioconjugates signal amplification electrochemical biosensing nanomaterials biomolecules

Nanobioconjugates are hybrid materials that result from the coalescence of biomolecules and nanomaterials. They have emerged as a strategy to amplify the signal response in the biosensor field with the potential to enhance the sensitivity and detection limits of analytical assays. This critical review collects a myriad of strategies for the development of nanobioconjugates based on the conjugation of proteins, antibodies, carbohydrates, and DNA/RNA with noble metals, quantum dots, carbon- and magnetic-based nanomaterials, polymers, and complexes.

## 1. Introduction

Nanochemistry is an emerging research field in the border of chemistry and nanoscience that involves a cross-disciplinary convergence of physical, biological, material sciences, and engineering for multiple purposes [1]. For example, nanochemistry-based nano-bioplatforms exploit natural biomimetic systems that connect chemical and biological systems with nanotechnology and study how such converging technologies help to achieve a better understanding of phenomena at the nanoscale [2][3][4]. With the advent of these emerging research fields, it has been possible to rapidly advance nanobioconjugate architectures with potential in a myriad of cross-disciplinary practical applications [5][6][7][8]. The development of nano-bio-constructs involves several chemical modifications on nanometer scaled structures, of which the properties are size, shape, self-assembly and defects dependent, while features are explained and well-studied in the fields of nanobiotechnology and nanochemistry.

Over the past years, nanobioconjugates have been probed as drug delivery systems, imaging and contrast agents, theranostic platforms, and for purification and concentration of biomolecules. They have received considerable attention in biosensing systems as amplifiers of the resultant signal. Nanobioconjugates are hybrid nano(bio)materials that result from the integration among nanomaterials (NMs) and biomolecules [9]. The development of these hybrid systems aims to get new materials with improved properties concerning each of their

components acting alone [10]. Each component contributes to the hybrid with a unique property or function that is missing in the other one. Nanobioconjugates are having a significant impact on the development of theranostic (therapeutic and diagnostic) tools in the biomedicine field [11][12][13][14][15][16] and have particular potential to revolutionize diagnostic approaches. Limitations of the nanobioconjugates are related to the uncontrolled number of affinity biomolecules that can be linked to the nanostructure, which leads to a variety of unwished phenomena [17]. For instance, a large number of biomolecules linked to nanostructures leads to hindered biochemical activity, alteration of the targeting and biomolecule properties and receptor cross-link [17][18]. Conversely, undesirable multivalent interactions and associated cooperative binding become insignificant if nanostructures have a proper number of linked biomolecules [17].

Within the nanobioconjugates development process, there are some features of the nanomaterials synthesis and the biomolecules coupling that must be controlled to reach stable hybrid materials. The nature of the precursors, their interactions and reagents ratio, the use of surfactants, temperature, time and stirring conditions, among other parameters of the synthesis process, impact on nanomaterial characteristics and their preferential crystal growth [19]. Nanomaterials may present defects depending on the synthesis method, including non-uniform surfaces, edges, lattices, and vertices that serve as points for the enhanced catalysis and anchoring of biomolecules. Bioconjugation employs many nanochemistry-based approaches. For example, carboxylic groups from graphene oxide (GO) can bind covalently aminated biomolecules [20][21]. Different crystalline orientations of gold nanosurfaces chemisorb thiol groups naturally from proteins, peptides, DNA strands, and alkyl organic compounds to form self-assembled monolayers (SAMs), among many other examples of bioconjugation [22][23]. Figure 1A highlights eight different nanobioconjugate configurations [1][10][21]. In the simplest format, the biomolecules might interact directly with the nanostructures (NSs). In more complex formats, the NSs surround or encapsulate the biological components of the nanobioconjugates. Target refers to the (bio)molecule of interest. Bioreceptors, also named ligands, are any kind of molecule that binds to a specific target commonly linked to the transducer, NS, or NM surfaces. Core and shell layers refer to the inner and outermost parts of NSs or NMs. The latter one is commonly bioconjugated with ligands when developing nanobioconjugates and assembling biosensors [1][10][21]. Figure 1B represents a NP decorated with diverse functional biomolecules such as nucleic acids, proteins, drugs, peptides, antibodies, enzymes and others [1][21]. Choosing the bioconjugation strategy is important and depends not only on nanomaterial composition, structure, and available functional groups but on the type of biological molecule, its size, chemical composition, and the requirements of the final application. Figure 1C shows four general conjugation strategies to link biomolecules to NM surfaces [21][23]. Pre- and post-bioconjugation physicochemical metrics include NM size, morphology and aspect ratio, aggregation/agglomeration state, purity, chemical composition, surface characteristics, ζ potential, surface area, and stability, as well as solubility, structure, orientation, and activity of the biomolecule [1][10][21]

## 2. Characterization of Nanobioconjugates

There are many physicochemical and bioconjugation metrics that are of interest in the characterization of nanobioconjugates. They include purity, size, shape, particle or conjugate mass, aspect ratio, surface area,

polidespersity and colloidal stability. Composition, surface properties, ζ potential and hydrodynamic radius, are other usual parameters to be considered when studying nanobioconjugates. Biomolecular orientation within the nanobioconjugate and activity, affinity, or avidity of the final conjugate for the target analyte is also necessary for interrogation . Dynamic light scattering (DLS) [24], electrophoretic light scattering (ELS) microscopy [25], spectroscopy [25][26], and thermal [27] techniques are the most used for nanobioconjugates characterization and are described as follows.

Scattering techniques give quantitative information about the size, shape, charge, distribution and concentration based on the interaction of incident radiation with colloidal particles and nanobioconjugates. Among them, DLS is one of the most employed techniques for nanobioconjugates characterization. This technique gives information about the size and concentration of nanoparticles measuring the hydrodynamic particle size. Brownian motion allows for the estimation of their diffusion coefficient, which is directly correlated with the hydrodynamic radius by the Stoke–Einstein equation. Analysis of the sample is comparatively rapid, simple, cheap, non-invasive, and non-destructive but not that straight forward when the samples are polydisperse, making necessary microscopy techniques for more accurate characterization of such samples . ELS is a measure of the ζ potential and gives information about the net superficial charge of nanoparticles or nanobioconjugates. The ζ potential is determined by applying an electric field to the sample where the velocity at which nanoparticles move toward an electrode of opposite charge is proportional to the ζ potential. It is indicative of the nanobioconjugates stability, which magnitude is correlated with the repulsion interactions and steric hindrance effects among adjacent charged particles in the colloidal suspension. The measurement of the ζ potential helps to determine if the bioconjugation process took place by taking into account the chemical nature of biomolecules .

X ray diffraction (XRD) is very useful to give information about the crystalline structure of the samples. This technique is powerful for the characterization of nanomaterials embedded inside biological matrixes or nanobioconjugates. The d-spacing analysis (the distance between crystallographic planes) is a parameter whose magnitude changes after a biomolecule is immobilized onto a nanomaterial and thus can be used to investigate the biomolecule orientation .

Microscopic techniques are based on the sample characterization by the use of light, electrons, and scanning probes. Scanning electron microscopy (SEM) gives information about surface topography and composition by the collection and processing of signals as a result of electrons striking the sample. SEM may have a resolution from 10 µm to 10 nm, but in some cases, the resolution can be down to 1 nm, depending on the equipment setup, operating parameters and sample material. The sample surface needs to be conducive to facilitate the microscopy analysis, usually achieved by depositing a conductive coating over the material before the SEM observation. Moreover, energy dispersive X-ray (EDX) can be employed under SEM analysis to determine the chemical composition of the sample. The released energy through photoemission in SEM-EDX depends on the electron configuration of the atoms and its collection allows the establishment of the elemental sample composition [28]. In transmission electron microscopy (TEM), a beam of electrons overpasses the sample to form an image. TEM may give information about the sample core, including biomolecules or nanobioconjugate-containing nanomaterials. The sample thickness must be less than 100 nm to reach the signal-to-noise ratio needed for high contrast, thanks to

the very strong incident beam of electron-sample interactions. TEM provides information about morphology, crystallographic degree, crystallographic planes, nanomaterials defects, etc., based on analysis by diffraction, spectroscopic methods, and imaging. High-resolution scanning transmission electron microscopy (HR-STEM) may resolve at the atomic level, depending on the medium that supports the particles [29]. Atomic force microscopy (AFM) operates through a scanning probe and gives information about the topography, size and shape of the nanomaterials and biomolecules, as well as adhesion and other interactions in the nanobioconjugates . Unlike SEM and TEM, AFM may image conductive and nonconductive samples in noncontact (static) and contact (dynamic) analysis by different probes commercially available.

Spectroscopic techniques take advantage of the electromagnetic radiation and its interaction with the samples that result in an absorption or emission spectrum that is directly dependent on wavelength and can be correlated with the size of nanobioconjugates and interactions among them. Ultraviolet and visible spectroscopy (UV-Vis) measures the interaction between electromagnetic waves and samples, giving information about the emitted or absorbed electromagnetic radiation by atomic or molecular species. The energy is supplied to the sample in the form of heat, light or chemicals. Each molecule absorbs the energy with a characteristic frequency and emits radiation, which intensity is a function of the wavelength. The spectroscopic analysis comprises atomic- and molecular-spectrochemical analysis and emission and absorption spectrum analysis. These techniques are used for rapid estimation of the size of the nanoparticles and nanobioconjugates by optical changes coming from collective oscillations and from characterizing chromogenic molecules or materials. UV-Vis spectroscopy is a fast, cheap, simple, non-destructive, and easy-to-operate technique [30].

Fourier transformed infrared spectroscopy (FT-IR) is the choice for rapid and easy characterization of functional groups of nanomaterials and nanobioconjugates. FT-IR radiation represents the molecular absorption and transmission as a result of the vibrational stretching and bending of molecules from the nanobioconjugates that create a fingerprint of a sample. FTIR is a non-destructive analysis technique where the intensity of peaks is directly correlated with the number of functional groups in the sample. It is a very useful technique for nanobioconjugates characterization in which the bioconjugation process is evaluated by comparing the spectrum before and after bioconjugation [31].

Electrochemical characterization (EC) consists of a set of powerful tools to evaluate and characterize the capacity of nanomaterials to be used mainly in energy storage and sensor applications. The EC is based on the evaluation of the mechanism involved in electron transfer, electron and mass transport and electrolyte behavior. EC techniques include cyclic voltammetry (CV), chronoamperometry (CA), chronopotentiometry (CP), galvanostatic charge-discharge (GCD), and electrochemical impedance spectroscopy (EIS), among others. EC studies the electrochemical performance of nanomaterials and nanobioconjugates under settled electrochemical conditions [32].

## 3. Nanobioconjugates in Biosensing

Biosensing refers to (bio)systems that can detect organisms, target analytes (biomolecules), and their biological activity [33][34] through electrical, thermal or optical signals, among other transduction mechanisms [35]. Biosensors are analytical devices that utilize a biological component in direct contact with a solid platform (transducer), which selectively respond to an analyte in a concentration-dependent manner. The resultant signal from the specific biomolecular interaction is read and registered in a simple way [36][37][38]. A biosensor must be designed to be versatile and easy to operate and have high-throughput, rapidity and accuracy [39]. Biosensors are labeled or label-free, depending on whether they use a mark or not to evidence a biorecognition event. Label-free biosensor refers to biosensing systems that only require one recognition element that reduces the assay time, reagent cost and the platform assembly but is restringed when the target concentration is too low.

In contrast, labeled biosensors can amplify the signal by incorporating nanobioconjugates as signaling tags [40]. In labeled-biosensor approaches, the target may be trapped in between a capture and a signal bioreceptor in a sandwich-like format. Whereas most of the capture bioreceptors are attached to nanostructured solid supports, electrodes, or chips, the signal bioreceptors are attached to some signaling tags, such as fluorophores, enzymes or nanomaterials. Signaling tags may have different binding sites, which enhance the signal and reduce the background [40][41], thus leading to an amplified response. Signal amplification takes advantage of the signaling tag, having more than one signal amplifier by bioreceptor in the same format. Signal amplification may also come from modified transducer platforms with electrodeposited materials or polyelectrolytes, which increase electron transfer in electrochemical biosensors and, in the presence of mediators, communicate with the nanobioconjugates-based signaling tags [42][43][44].

## 4. Current Challenges and Future Perspectives in Nanobioconjugates Development

We have reviewed several biosensing reports that include nanobioconjugates for signal amplification in multiple formats. They have outstanding performance and the potential to achieve high sensitivity and ultralow limits of detection in nanobioconjugate-based assays. Their features are compatible with multiplexing and miniaturization, as well as portability and low volume of samples and reagents. However, there are still some challenges to face before implementing such reporters in biosensors in a real scenario. For example, biomarkers are commonly present in biological fluids in extremely low concentrations [45], so their detection and monitoring require highly sensitive devices.

The use of nanostructured materials in the development of electrochemical biosensing platforms offers the opportunity of a wide range of modifications with different bioreceptors and thus specific detection of a myriad of target biomolecules. All parameters involved in the nanobioconjugates development need to be systematically optimized and standardized before being incorporated in electrochemical biosensing platforms for the detection of the target molecules with high sensitivity and specificity. In this context, nanobioconjugates stability must be well established to ensure nanobioconjugates performance and reproducibility of biosensors. Parameters influencing the long term stability of nanobioconjugates such as nanomaterial geometric shape [46], ionic strength [47], pH [48], and temperature [49] need to be optimized. The need to strictly control the number of affinity biomolecules in a

nanobioconjugate to avoid unwished phenomena is still a challenge. An excessive number of biomolecules linked onto nanostructured surfaces may hinder their biochemical activity, which alters their targeting ability by cross-linking with other molecules . Conversely, multivalent interactions and associated cooperative binding become insignificant whether nanostructures have a lower number of biomolecules attached to them .

Yet, nanobioconjugates have tremendous potential for the development of biosensing platforms and devices of superior performance, with an excellent capacity for enhancing the signal amplification processes of biorecognition events. They have many advantages as compared with conventional assays. Although conventional assays are ordinarily used, many of them are time-consuming and require robust instrumentation, which hinders timely and accurate target detection and quantification [50]. Advantages of nanobioconjugate-based assays include their relatively lower cost and faster analysis time, and the fact that they do not require expensive equipment and there is no need for well-trained personal. The aforementioned features make such nanoplatforms hold the potential to be implemented for analysis in place, even in remote settings.

Two-dimensional nanomaterials are emerging nanomaterials of enhanced physical, chemical and optical properties as compared to their bulk counterparts [51], which make them promising for the development of nanobioconjugates. For instance, their high surface area allows for hosting thousands of biomolecules in a proper nano-environment that promotes the stability and activity of biomolecules [51][52]. Implementation of 2D nanomaterials in nanobioconjugate assemblies opens opportunities towards keep increasing sensitivity and stability and decreasing the LOD of bioassays where they are assembled.

Overall, nanobioconjugates offer the possibility to detect different target biomolecules with high specificity and sensitivity in less time and in a straighter forward way as compared with standard assay methods. Such unique features, along with versatility, accurate quantification, and amenability for multiplexing and miniaturization, are paving the way towards the development of new enhanced nanobioconjugate-based device alternatives. Progress remains to be made for positioning this technology in the market. It requires joined efforts from cross-disciplinary fields that involve nanochemistry and nanobiotechnology. However, it is clear that nanobioconjugates are at the forefront of research in many fields, not only as reporters in signal amplification in biosensors, but as nanocarrires for targeted drug delivery and contrast agents in biomedical imaging among many others, always searching for novel and new opportunities depending on the final application.

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